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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/599,087	06/21/00	LUETHY	R 00,450

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/599,087	Applicant(s) LUETHY ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sh et with the correspond nc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *9,12-45 and 49-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-59* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 and 10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-59 are pending in the application.

2. The election with traverse of Group 2 filed on May 25, 2001 in Paper No. 9 is acknowledged and has been entered. Claims 9, 12-45, and 49-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-8, 10, 11, and 46-48 are currently under prosecution.

Election/Restrictions

4. Applicant's election with traverse of Group 2 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that searching Groups 1 and 2 would not constitute a serious burden. This is not found persuasive because the search required for examination of Group 1 is not coextensive with the search required for examination of Group 2. Different searches are required for each group and different issues pertaining to the patentability of each group must be considered.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

5. Claims 1-8, 10, 11, and 46-48 are objected to because of the following informalities: The claims are drawn in the alternative to a non-elected invention(s). Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 10, 11, and 46-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 4 or a fragment thereof that encodes a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 5 or a fragment thereof, respectively, does not reasonably provide enablement for an isolated nucleic acid molecule comprising a nucleotide sequence that hybridizes under moderately or highly stringent conditions to the complement of the nucleotide sequence set forth in SEQ ID NO: 4 or an isolated nucleic acid molecule encoding an isolated polypeptide comprising an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to an isolated nucleic acid molecule comprising the polynucleotide sequence set forth in SEQ ID NO: 4 or a fragment thereof, which encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 or a fragment thereof, respectively. The claims are also drawn to an isolated nucleic acid molecule that hybridizes to the complement of the nucleotide sequence set forth in SEQ ID NO: 4. The claims are also drawn to an isolated nucleic acid molecule encoding a polypeptide or a fragment thereof comprising an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. The claims also encompass an isolated nucleic acid molecule encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 wherein at least one modification has been made, including deletions, insertions, substitutions, and

truncations. Therefore, even though the claims recite the limitation that the polypeptide encoded by the claimed nucleic acid molecule have an activity of the polypeptide that consists of the amino acid sequence set forth in SEQ ID NO: 5, the claims read on any nucleic acid molecule that encodes a polypeptide, because any polypeptide will have an activity of the polypeptide that consists of the amino acid sequence set forth in SEQ ID NO: 5. For example, any polypeptide will have antigenic activity and most, if not all polypeptides will be active substrates for a protease. Consequently, given the broadest reasonable interpretation, the claims encompass any and all isolated nucleic acid molecules that encode a polypeptide.

The specification teaches the polynucleotide sequence (i.e., SEQ ID NO: 4) of a cDNA molecule that encodes an amino acid sequence of a human protein, designated Secs-1, which consists of the amino acid sequence set forth in SEQ ID NO: 5 (pages 84-86 and Figures 1-3). The specification also teaches the polynucleotide sequence of a genomic fragment that encodes the Secs-1 polypeptide (Figure 4). In examples 1-5, respectively, the specification teaches methods for cloning the gene encoding Secs-1, methods for analyzing the expression of the gene encoding Secs-1, methods for producing the Secs-1 polypeptide, methods of producing an antibody that binds the Secs-1 polypeptide, and methods for producing a transgenic mouse expressing human Secs-1 (pages 84-92). Finally, in the remaining examples, the specification discloses conventional methods that might be used to characterize the biological activity of Secs-1, which include the use of transgenic mice expressing the human Secs-1 polypeptide (pages 92-94).

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims. The reason for this conclusion is set forth below:

As noted above, the breadth of the claims actually encompasses any and all nucleic acid molecules encoding a polypeptide. Clearly the teachings of the specification cannot be extrapolated to the enablement of claims with such breadth. More narrowly interpreted, the claims encompass nucleic acid molecules that encode variants of the Secs-1 polypeptide, which differ in amino acid sequence from the

polypeptide sequence of SEQ ID NO: 5. For example, the claims encompass nucleic acid molecules that encode polypeptides that are only about 70% identical to SEQ ID NO: 5. These polypeptides will necessarily differ from SEQ ID NO: 5 in amino acid sequence at about 30 out of every 70 positions. Also, the claims also encompass nucleic acid molecules that encode polypeptides comprising only fragments of the amino acid sequence set forth in SEQ ID NO: 5. On the other hand, it is noted that nucleic acid molecules that encode polypeptides with relatively more moderate variations in the amino acid of SEQ ID NO: 5 are encompassed by the claims. For example, claim 15 encompasses a nucleic acid molecules that encodes a polypeptide that differs from SEQ ID NO: 5 at only one position by the conservative substitution of one amino acid for another that has similar chemical properties as the one being replaced.

The skilled artisan cannot accurately predict the inherent effects of dissimilarity in the amino acid sequences of polypeptides upon protein structure and function. Bowie, et al (*Science* **257**: 1306-1310, 1990) teach that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Bowie, et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2).

Burgess, et al (*Journal of Cell Biology* **111**: 2129-2138, 1990) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. This reference teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding,

receptor binding and biological activity of the protein. As another example of the unpredictability in the art, Lazar et al (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. For emphasis, it is noted that Lazar, et al teaches that the conservative substitution of aspartic acid for glutamic acid causes a substantial loss of the protein's activity.

The specification teaches that the claimed nucleic acid molecule can be used to produce the Secs-1 polypeptide and variants or fragments thereof. However, the physiologic activity of the Secs-1 polypeptide encoded by the claimed nucleic acid molecule is not disclosed in the specification. Moreover, the specification does not specifically identify an activity of the Secs-1 polypeptide, which is encoded by the claimed nucleic acid molecule. For that matter, the specification fails to teach the physiologic activities of the polypeptide encoded by the claimed nucleic acid molecules that vary in polynucleotide sequence from SEQ ID NO: 4. So apart from teaching methods for determining the non-specific activities of the polypeptide encoded by the claimed nucleic acid molecules, which are obviously characteristic of all polypeptides (e.g., antigenicity), the specification does not enable the use of the Secs-1 polypeptide, *per se,* or any variant or fragment thereof.

Considering the teachings of the references cited above, it is apparent that even a single amino acid substitution could often dramatically affect the biological activity and the structure-function characteristics of a protein. Therefore, it is clear that one skilled in the art cannot immediately conclude that any of the claimed variants of the Secs-1 polypeptide will have an activity, including antigenicity that is identical or even similar to the Secs-1 polypeptide. The specification does not teach how the claimed variants of the Secs-1 polypeptide can be used. Based upon the teachings of Bowie, et al, Burgess, et al, and Lazar, et al, it is especially clear that one skilled in the art cannot predict whether the broadly claimed nucleic acid molecules encoding proteins that have an amino acid sequence that is less than 100% identical to SEQ ID NO: 5 can be used in accordance with the disclosed utilities in the specification, because it is not

immediately evident or obvious that the proteins will be functionally identical or similar to the polypeptide of SEQ ID NO: 5.

In view of the above, it is apparent that one skilled in the art cannot practice the claimed invention with a reasonable expectation of success without first embarking upon a course of extensive and therefore undue experimentation. Therefore, the specification fails to meet the requirements of 35 USC § 112, first paragraph as it does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with the claims.

8. Claims 46-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition comprising a nucleic acid molecule or a fragment thereof encoding a polypeptide or a fragment thereof, respectively, which comprise an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. The claims encompass viral vectors, which can be used for gene therapy.

The specification teaches that which is set forth in the 35 USC § 112, first paragraph rejection above. The specification also teaches conventional wisdom regarding the production and use of pharmaceutical compositions comprising nucleic acid molecules that encode therapeutically active polypeptides (pages 66-72). On pages 72-83, the specification discloses conventional wisdom regarding methods involving homologous recombination and gene therapy. The specification discloses potential therapeutic uses for the claimed pharmaceutical compositions on pages 83-84.

The teachings of the specification, however, cannot be extrapolated to the enablement of the invention commensurate in scope with the claims. The reason for this conclusion is that there is insufficient guidance and exemplification in the specification that would serve to enable one skilled in the art to make and/or use the invention with a reasonable expectation of success. Furthermore, in the absence of

exemplification and based only upon the teachings of the specification, one skilled in the art cannot predict whether the claimed invention can be made and used effectively to prevent, treat, or diagnose a disease or any other abnormal physiologic condition. Therefore, the skilled artisan would have to first perform extensive experimentation in order to determine whether the claimed invention can be made and used effectively.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). The factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

It is well known that the art of drug discovery is highly unpredictable. For example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential therapeutic agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs).

Clearly one skilled in the art cannot predict whether a pharmaceutical composition comprising a nucleic acid molecule encoding the human Secs-1 polypeptide can be used therapeutically. Of course, for that matter, one skilled in the art cannot predict whether a pharmaceutical agent comprising a nucleic acid molecule encoding a variant, homolog, ortholog, fragment, derivative, or fusion of the Secs-1 polypeptide can be used therapeutically, since any alteration or modification in the sequence of the polypeptide may alter the activity of Secs-1. The teachings of Burgess, et al (cited supra) and Lazar, et al (cited supra), which were referenced in the 35 USC§ 112, first paragraph rejection above provide evidence of this latter fact. Consequently, the effects of putative pharmaceutical agents, such as nucleic acid molecules encoding the Secs-1 polypeptide or derivatives and variants thereof, can only be determined

empirically. Even in the presence of scientific data suggesting that a pharmaceutical agent can be used efficaciously, there is need for caution. The effects of a given pharmaceutical agent upon a culture of cells or an experimental animal may be entirely different from the effects of the agent upon a human patient. For example, Bergers, et al (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers, et al comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical agent that comprises the Secs-1 polypeptide or a derivative or fragment thereof to a subject in need of therapy. Rather than ameliorating the disease, it is quite possible, in light of the teachings of Bergers, et al, that the agent may promote the progression of the disease.

Nevertheless, the specification does not specifically teach how the claimed pharmaceutical compositions are to be used. Moreover, the specification does not specifically teach which diseases or abnormal physiologic conditions can be prevented, treated, or diagnosed using the claimed pharmaceutical compositions. In fact, in the absence of sufficient information regarding the activity of the Secs-1 polypeptide it is difficult to even imagine which diseases might be treated or diagnosed using the invention. Actually, the specification is entirely deficient in teaching an association between the Secs-1 polypeptide and the etiology or pathogenesis of any one disease. There may be no such association, in which case, while the specification is clearly not enabling, the invention may not have utility. Based only upon the disclosure, certainly one skilled in the relevant art cannot predict whether the Secs-1 polypeptide is involved in the etiology or pathology of a specific disease. De Plaen, et al (*Immunogenetics* **40**: 360-369, 1994) review the expression of twelve genes of the MAGE family. De Plaen, et al teach that six of the members of the gene family are expressed at a high level in a number of tumors of various histological types and five were very weakly expressed in

all samples tested, but one, MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (see page 367, column 1). Obviously, therefore, not all MAGE family proteins are associated with tumors and it is not apparent what, if any, association the weakly expressed MAGE proteins have with tumors. Accordingly, in light of the teachings of De Plaen, et al, it is clear that one skilled in the relevant art would not conclude that a given nucleic acid encoding a protein is associated with neoplastic disease despite the fact that genes encoding related family members might be. Therefore, for the reason set forth in this example, one skilled in the relevant art cannot predict, based upon the information disclosed in the specification, that the gene encoding the Secs-1 polypeptide or the Secs-1 polypeptide, itself, has any association with the etiology or pathology of cancer or any other abnormal condition.

It is important to note that the actual biologic activity of Secs-1 polypeptide is not disclosed in the specification. Nevertheless, even if it were so that the activity of Secs-1 polypeptide was reasonably defined, many polypeptides are known to have entirely different effects upon different cell types. For example, Baxter, et al (*Journal of Biological Chemistry* **274**: 9539-9547, 1999) teaches that the activity of TNF-α is ambiguous since it can induce a cell to proliferate or it can have quite the opposite effect, causing a cell to undergo programmed cell death (i.e., apoptosis). Thus, it is reasonably clear that the skilled artisan cannot practice the claimed invention with a reasonable expectation of success, because the specification fails to demonstrate that the pharmaceutical composition can be used effectively to treat any one disease or abnormal condition. Certainly, in view of the teachings of Baxter, et al, one skilled in the art cannot predict whether the invention can be used effectively and would therefore be forced to perform undue experimentation in order to practice the invention.

The disclosure suggests that the invention can be used as a DNA vaccine to stimulate an immune response directed against cells that express Secs-1. With regard to DNA vaccines, *per se*, considerable limitations are known in the art, which substantially limit the efficacy of such therapeutic approaches. Bodey, et al (*Anticancer Research* **20**: 2665-2676, 2000) teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of

anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). In the abstract Bodey, et al disclose:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

Clearly, if a tumor does not express the antigen that is specifically bound by the antibody the use of a pharmaceutical composition comprising that antibody will not be effective. However, as Bodey, et al teach, use of such a pharmaceutical composition may only serve to select against tumor cells that express the antigen, while promoting the growth of tumor cells that do not express the antigen. Furthermore, since normal epithelial cells express Secs-1 polypeptide, as the specification teaches, it is not clear that immune cells stimulated by the claimed pharmaceutical composition can selectively target diseased cells. Thus, while the efficacy of the claimed pharmaceutical composition cannot be predicted or determined without undue experimentation, clearly one skilled in the art would have reason to doubt that the pharmaceutical composition can be used effectively.

In addition to vaccines, the claims also encompass a variety of other types of pharmaceutical compositions that might be used in different therapeutic strategies. However, as with vaccines, there is absolutely no factual evidence that these pharmaceutical compositions can be used effectively. Moreover, most, if not all of these therapeutic strategies are known to be subject to significant limitations. In particular, it is noted that attempts to develop therapeutic strategies, which involve vectors that encode polypeptides, ribozymes, or antisense DNA (i.e., gene therapy), are subject to

very significant limitations. Only one study known in the art of gene therapy has yielded encouraging results and in general investigators have met with little success due to many challenging problems, which include, but are not limited to a lack of specificity, an inability to maintain high levels of expression, and immunogenicity.

In summary, in the absence of exemplification and sufficient guidance, the specification clearly fails to meet the enablement requirements of 35 USC § 112, first paragraph. Given only the teachings of the specification, because of the high degree of unpredictability in the art, the skilled artisan cannot make and/or use the invention with a reasonable expectation of success. Accordingly, one skilled in the art would be forced to perform extensive and undue experimentation in order to practice the invention successfully.

9. Claims 1-8, 10, 11, and 46-48 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description sets forth SEQ ID NO: 4, which is the polynucleotide sequence of a cDNA encoding the human polypeptide designated Secs-1. In addition, the written description includes a disclosure of the polynucleotide sequence (i.e., SEQ ID NO: 8) of a genomic DNA molecule that encodes the human Secs-1 polypeptide (Figure 4). The written description also set forth in SEQ ID NO: 1, the polynucleotide sequence of a cDNA encoding an ortholog of the human Secs-1 polypeptide, namely the mouse Secs-1 (or muSmac2) polypeptide.

The claims, however, encompass a far broader genus of nucleic acid molecules, which encode polypeptides having at least 70% identity to the amino acid sequence set forth in SEQ ID NO: 5. For example, the claims encompass naturally occurring alleles that encode variants of Secs-1 and alternatively spliced messenger RNA molecules, which might encode isoforms of Secs-1. In fact, claim 2 specifically recites a limitation

that the claimed nucleic acid molecule encode an allelic variant or splice variant of a nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO: 5.

The disclosure of three species of the claimed genus of nucleic acid molecules encoding Secs-1-like polypeptides, namely SEQ ID NO: 1, 4, and 8 is considered insufficient to meet the written description requirement of 35 USC § 112, first paragraph for the following reason:

The structures and polynucleotide sequences of the vast majority of these congeneric species of nucleic acid molecules encoding Secs-1-like polypeptides are not disclosed in the specification. More particularly, the structures and polynucleotide sequences of the claimed nucleic acid molecule encoding polypeptides that comprise the amino acid sequence of an allelic variant or splice variant of the amino acid sequence of SEQ ID NO: 5 are not disclosed. In accordance, the claimed subject matter is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

The findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 are clearly relevant to the instant invention. *Fiers v. Revel* and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.* found that adequate written description requires more than a mere statement that it (a nucleic acid) is part of the invention. The nucleic acid itself is required; or by inference, in the instant case, the claimed polynucleotide sequence of an allelic variant or splice variant of the polynucleotide sequence of SEQ ID NO: 4 itself is required.

Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA [molecule] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The findings of the court are clearly applicable to the claimed naturally occurring nucleic acid sequences. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotide sequences or for that matter, of the polypeptides encoded by the claimed genus of nucleic acid molecules.

Claim 10 recites the limitation that the claimed nucleic acid molecules comprise promoter DNA other than the promoter DNA for the native Secs-1 polypeptide. However, the structure and sequence of the native promoter for the human *Secs-1* gene is not disclosed. Neither is the structure and sequence of any other native promoter for a gene encoding an ortholog of the human Secs-1 polypeptide disclosed. Therefore, the written description is devoid of information necessary to distinguish the promoter DNA for the native Secs-1 polypeptide from other promoter DNA. The inadequacy of the written description suggests that Applicant did not have possession of the invention at the time the application was filed.

With regard to the Secs-1 polypeptide, in particular, there is no description of the conserved regions that are critical to the structure and function of the polypeptide encoded by the claimed genus of nucleic acid molecules. In fact, as set forth in the 35 USC § 112, first rejection above, the specification does not include a description of the physiologic activity of the Secs-1 polypeptide. Furthermore, there is no description of the sites at which variability may be tolerated and there is no information regarding the

relation of the polypeptide's structure to its function. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed by the claims. Therefore, because the amino acid sequences of the polypeptides encoded by the claimed genus of nucleic acid molecules are not disclosed and because no identifying characteristic or property is provided, the skilled artisan certainly cannot envision the structures and sequences of the claimed nucleic acid molecules encoding those polypeptides. Moreover, one skilled in the art cannot reasonably identify those nucleic acid molecules that are encompassed by the claims. In other words, the specification fails to describe the common attributes or characteristics that identify members of the genus and for this reason, the disclosure is considered to be inadequate to meet the written description requirements of 35 USC § 112, first paragraph.

Additionally, the absence of sufficient disclosure to meet the written description requirement of 35 USC § 112, first paragraph suggests that Applicant did not have possession of the invention at the time the application was filed. Furthermore, Applicant is reminded that conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method for isolating and characterizing a nucleic acid molecule. It is equally, if not more apparent that Applicant was not in possession of the claimed pharmaceutical compositions at the time the application was filed. For example, no specific teachings or disclosures are apparent in the specification that describes the multitude of viral vectors, which comprise the claimed genus of nucleic acid molecules. There is simply no factual evidence of record that would serve to convince the skilled artisan that Applicant had possession of the invention at the time the application was filed.

In summary, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method for isolating the gene or messenger RNA encoding the allelic or splice variants of SEQ ID NO: 5. The polynucleotide sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. With the exception of SEQ ID NO: 1, 4, and 8, the skilled artisan cannot

immediately envision the detailed structure of the encompassed naturally occurring nucleic acid sequences. Certainly, the skilled artisan cannot envision the structures of naturally occurring alleles or alternatively spliced messenger RNA molecules encoding a Secs-1-like polypeptide. Consequently, the disclosure is insufficient to meet the written description requirement of 35 USC 112, first paragraph and to support the generic claims in accordance with *The Guidelines for Examination of Patent Applications* (66 FR 1099-1111, 5 January 2001).

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-8, 10, 11, and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 10, 11, and 46-48 are vague and indefinite because claims 2 and 3 recite the phrase "has an activity". The use of the phrase renders the claims vague and indefinite because it is unclear to which activity the claim refers and therefore it is unclear how one of ordinary skill in the art can determine the activity to which the claim refers. Furthermore, the claims are so broad as to be vague. Accordingly one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claims 1-8, 10, 11, and 46-48 are indefinite because claims 1, 2, and 3 recite the phrase "the DNA insert in ATCC Deposit Nos. PTA-1753". The use of the phrase renders the claims indefinite because it is not clear to which DNA insert the claim refers. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending one or more independent claims of the elected invention to recite, for example, the phrase "wherein said insert comprises the polynucleotide sequence set forth SEQ ID NO: 4, which encodes the amino acid sequence set forth in SEQ ID NO: 5" can obviate this rejection.

Claims 1-8, 10, 11, and 46-48 are also indefinite because claim 1 recites the phrase "hybridizes under moderately or highly stringent conditions". Moderately and highly stringent conditions are not specifically defined in the claim. Therefore, the claim encompasses conditions that range in stringency from very permissive to very selective and the specification does not provide a standard for ascertaining the requisite degree of stringency. Furthermore, it is unclear whether the claim requires the nucleotide sequence to hybridize specifically and selectively to the complement of (a) – (c) or merely hybridize non-specifically or non-selectively. Consequently, one of ordinary skill in the art is not be reasonably apprised of the metes and bounds of the invention. Amending claim 1 to recite the specific conditions and to recite, for example, the phrase "a nucleotide sequence that specifically and selectively hybridizes under [specific conditions]" can obviate this rejection.

Where a trademark or trade name is used in a claim, MPEP 7.35.01 reads, "the claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material product. On the other hand, a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name." See *Ex parte Simpson*, 218 USPQ 1020 (PTO Board of Patent Appeals and Interferences, 1982). Therefore, in the instant case, claim 11 is indefinite because of the use of the trademark name "BestFit™" to identify a fixative. Amending the claims to delete the trademark name "BestFit™" can obviate these rejections.

Claim 11 is also indefinite in the use of the terms "GAP", "BLASTP", "FASTA", "BLASTA", "BLASTX", "BestFix™", and the "Smith-Waterman" algorithm. These terms identify algorithms, which are subject to change, and are implemented by software programs that are further subject to change, thereby creating different versions. Accordingly, the result acquired when using the software programs that implement these algorithms might also change. Therefore, it is necessary to identify the algorithm and software by the version and the date of the version, so that one of ordinary skill in the art is reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 2, 3, and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by The FAPESP/LICR Human Cancer Genome Project (GenBank EST Database Accession No. AW351839, 1999), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 1).

The FAPESP/LICR Human Cancer Genome Project teach the polynucleotide sequence of an isolated nucleic acid molecule encoding an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. In fact, the amino acid sequence of the polypeptide encoded by the nucleic acid molecule of the prior art is 100% identical to the amino acid sequence set forth in SEQ ID NO: 5.

Because the polypeptide of the prior art has the same amino acid sequence as the claimed polypeptide, the polypeptide of the prior art will have an activity of the

polypeptide of SEQ ID NO: 5. This is an inherent property of the prior art polypeptide. Furthermore, the search engine used to determine the percent identity uses the Smith-Waterman algorithm.

All the limitations of the claims are met.

14. Claims 2, 3, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier, et al (GenBank EST Database Accession No. AA422178, 1997), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 2).

Hillier, et al teach the polynucleotide sequence of an isolated nucleic acid molecule encoding an amino acid sequence that is at least about 70% identical to the amino acid sequence set forth in SEQ ID NO: 5. In fact, the amino acid sequence of the polypeptide encoded by the nucleic acid molecule of Hillier, et al is 100% identical to the amino acid sequence set forth in SEQ ID NO: 5 over the region spanning from the amino acid at position 1 to the amino acid at position 76. Therefore, the isolated nucleic acid molecule of Hillier, et al encodes a polypeptide that is truncated at the C-terminus, encoding a fragment of SEQ ID NO: 5 comprising at least about 25 amino acid residues.

Because the polypeptide of the prior art has the same amino acid sequence as the claimed polypeptide, the polypeptide of the prior art will have an activity of the polypeptide of SEQ ID NO: 5. This is an inherent property of the prior art polypeptide. Furthermore, the search engine used to determine the percent identity uses the Smith-Waterman algorithm.

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over The FAPESP/LICR Human Cancer Genome Project (GenBank EST Database Accession No. AW351839, 1999), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 1).

Refer to the corresponding 35 USC § 102(a) rejection above for an analysis of the claims.

The FAPESP/LICR Human Cancer Genome Project teach that which is set forth in the 35 USC § 102(a) rejection above. However, the FAPESP/LICR Human Cancer Genome Project do not disclose a vector comprising the prior art nucleic acid, a host cell comprising said vector, or a process for producing the polypeptide encoded by said nucleic acid.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use an expression vector comprising the nucleic acid molecule of The FAPESP/LICR Human Cancer Genome Project so that the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 could be produced. Methods for construction of expression vectors, methods for introduction of expression vectors into eukaryotic and prokaryotic host cells, and methods for production of polypeptides encoded by expression vectors was conventional at the time the invention was made. One of ordinary skill in the art at the time the invention was made would have been motivated to make and use an expression vector comprising the nucleic acid molecule of The FAPESP/LICR Human Cancer Genome Project so that the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 could be produced, because the polypeptide could be used to produce antibodies that specifically bind the polypeptide and antibodies are useful tools for studying the biologic function of a given polypeptide.

Furthermore, the FAPESP/LICR Human Cancer Genome Project do not disclose that the prior art nucleic acid will hybridize under moderately or highly stringent conditions to the complement of the polynucleotide sequence set forth in SEQ ID NO: 4. However, one of ordinary skill in the art at the time the invention was made would have expected the prior art nucleic acid molecule to hybridize under moderately or highly stringent conditions to the complement of the polynucleotide sequence set forth in SEQ ID NO: 4. Therefore, the nucleic acid molecule of the FAPESP/LICR Human Cancer Genome Project appears to be the same as the isolated nucleic of the instant claims, absent a showing of non-obvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon Applicant to prove that the claimed nucleic acid molecules are functionally different than those taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) *and Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

17. Claims 1-8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier, et al (GenBank EST Database Accession No. AA422178, 1997), as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 2).

Refer to the corresponding 35 USC § 102(b) rejection above for an analysis of the claims.

Hillier, et al teach that which is set forth in the 35 USC § 102(b) rejection above. However, Hillier, et al do not disclose a vector comprising the prior art nucleic acid, a host cell comprising said vector, or a process for producing the polypeptide encoded by said nucleic acid.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use an expression vector comprising the nucleic acid molecule of Hillier, et al so that the polypeptide comprising the amino acid

sequence of SEQ ID NO: 5 could be produced. Methods for construction of expression vectors, methods for introduction of expression vectors into eukaryotic and prokaryotic host cells, and methods for production of polypeptides encoded by expression vectors was conventional at the time the invention was made. One of ordinary skill in the art at the time the invention was made would have been motivated to make and use an expression vector comprising the nucleic acid molecule of Hillier, et al so that the polypeptide comprising the amino acid sequence of SEQ ID NO: 5 could be produced, because the polypeptide could be used to produce antibodies that specifically bind the polypeptide and antibodies are useful tools for studying the biologic function of a given polypeptide.

Furthermore, Hillier, et al do not disclose that the prior art nucleic acid will hybridize under moderately or highly stringent conditions to the complement of the polynucleotide sequence set forth in SEQ ID NO: 4. However, one of ordinary skill in the art at the time the invention was made would have expected the prior art nucleic acid molecule to hybridize under moderately or highly stringent conditions to the complement of the polynucleotide sequence set forth in SEQ ID NO: 4. Therefore, the nucleic acid molecule of Hillier, et al appears to be the same as the isolated nucleic of the instant claims, absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon Applicant to prove that the claimed nucleic acid molecules are functionally different than those taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) *and Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

Conclusion

18. No claims are allowed.

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hillier, et al (GenBank EST Database Accession No. AA283751, 1997) teach a nucleic acid molecule that encodes a polypeptide that anticipates claims 9 and 14-17, as evidenced by a USPTO database search using SEQ ID NO: 5 as a query (see USPTO Search Report US-09-599-087-5.rst, result 4).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
July 17, 2001